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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/944,807	08/31/2001	Birgit Jung	1/1144	1468

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EXAMINER
KEMMERER, ELIZABETH

ART UNIT	PAPER NUMBER
1646	8

DATE MAILED: 02/06/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/944,807	JUNG ET AL.	
	Examiner	Art Unit	
	Elizabeth C. Kemmerer, Ph.D.	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 November 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-73* is/are pending in the application.

4a) Of the above claim(s) *11-64* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-10 and 65-73* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1-73* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *5* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Election/Restrictions

Applicant's election of Group I, claims 1-10 in part as they read on methods of determining whether a substance is an activator or inhibitor of an ILM receptor wherein the receptor comprises SEQ ID NO: 2 or generically claimed variants thereof, in Paper No. 7 (18 November 2002) is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claims 11-64 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in Paper No. 7.

Status of Application, Amendments, And/Or Claims

The amendment filed 18 November 2002 (Paper No. 7) has been entered in full. Claims 11-64 are withdrawn from consideration, as discussed above. Claims 1-10 and 65-73 are under examination to the extent that they read on methods of determining whether a substance is an activator or inhibitor of an ILM receptor wherein the receptor comprises SEQ ID NO: 2 or generically claimed variants thereof.

Claim Objections

Claims 1-9 and 65-71 are objected to because of the following informalities: These claims recite non-elected subject matter (receptors other than SEQ ID NO: 2 and generically recited variants thereof). Appropriate correction is required.

35 U.S.C. § 112, First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 6 and 70 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The claims are directed to a method of screening for activators and inhibitors of a transmembrane receptor, namely the receptor of SEQ ID NO: 2 or generic variants thereof, in a cell-free test system. The specification clearly discloses cell-based assay systems that are appropriate for this assay. However, no cell-free test systems are disclosed in the working examples. Also, no guidance is given in the specification as to what is required for a cell-free system to test a transmembrane receptor. The art also does not recognize cell-free systems that can test a transmembrane receptor. Due to the large quantity of experimentation necessary to work out how to use a cell-free test system to test a transmembrane receptor, the lack of direction/guidance presented in the specification regarding same, the absence of

working examples directed to same, the complex nature of the invention, the state of the prior art, the unpredictability of what would be required for such a system to work, and the breadth of the claims which fail to recite limitations of the components needed for a cell-free system, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

Claims 1-5, 7-10, 65-69, 71 and 73 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the recited methods wherein the FPRL-1 receptor comprises SEQ ID NO: 2, does not reasonably provide enablement for the methods reciting variants, mutants, or fragments of SEQ ID NO: 2. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex. While it is known that many amino acid substitutions are generally possible in any given protein the positions within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of success are limited. Certain positions in the sequence are critical to the protein's structure/function relationship, e.g. such as various sites or regions directly involved in binding, activity and in providing the correct three-dimensional spatial orientation of binding and active sites. These or other regions may also be critical determinants of

antigenicity. These regions can tolerate only relatively conservative substitutions or no substitutions (see Wells, 1990, Biochemistry 29:8509-8517; Ngo et al., 1994, The Protein Folding Problem and Tertiary Structure Prediction, pp. 492-495). However, Applicant has provided little or no guidance beyond the mere presentation of sequence data to enable one of ordinary skill in the art to determine, without undue experimentation, the positions in the protein which are tolerant to change (e.g. such as by amino acid substitutions or deletions), and the nature and extent of changes that can be made in these positions. Although the specification outlines art-recognized procedures for producing and screening for active muteins, this is not adequate guidance as to the nature of active derivatives that may be constructed, but is merely an invitation to the artisan to use the current invention as a starting point for further experimentation. Even if an active or binding site were identified in the specification, they may not be sufficient, as the ordinary artisan would immediately recognize that an active or binding site must assume the proper three-dimensional configuration to be active, which conformation is dependent upon surrounding residues; therefore substitution of non-essential residues can often destroy activity. The art recognizes that function cannot be predicted from structure alone (Bork, 2000, Genome Research 10:398-400; Skolnick et al., 2000, Trends in Biotech. 18(1):34-39, especially p. 36 at Box 2; Doerks et al., 1998, Trends in Genetics 14:248-250; Smith et al., 1997, Nature Biotechnology 15:1222-1223; Brenner, 1999, Trends in Genetics 15:132-133; Bork et al., 1996, Trends in Genetics 12:425-427). Due to the large quantity of experimentation necessary to generate the infinite number of derivatives recited in the claims and

possibly screen same for activity, the lack of direction/guidance presented in the specification regarding which structural features are required in order to provide activity, the absence of working examples directed to same, the complex nature of the invention, the state of the prior art which establishes the unpredictability of the effects of mutation on protein structure and function, and the breadth of the claims which fail to recite any structural or functional limitations, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

35 U.S.C. § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-4, 7-10, 65-68 and 71-73 rejected under 35 U.S.C. 102(b) as being anticipated by Takano et al. (1997, J. Exp. Med. 185:1693-1704).

Takano et al. teach a method comprising (a) applying a substance (LXA_4) to a cellular test system (CHO cells) which generates a measurable read-out (GTP hydrolysis) upon modulation of the human ILM receptor of SEQ ID NO: 2 and (b) comparing the level of the read-out of the test system to a control level, wherein a difference in levels indicates whether the substance is an activator or an inhibitor of the receptor. In this case, the LXA_4 was an inhibitor. See Figure 2A for SEQ ID NO: 2. See p. 1697, paragraph bridging left and right columns, for assay. Takano et al. further

teach that LXA_4 is an inhibitor of inflammation in a similar assay (p. 1699+, "*LXA_4 and 15-epi-LXA_4 Analogues Inhibit Mouse Ear Inflammation*").

35 U.S.C. § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 5 and 69 are rejected under 35 U.S.C. 103(a) as being unpatentable over Takano et al. in view of Hawkins et al. (U.S. Patent 5,811,520).

Takano et al. teach a method comprising (a) applying a substance (LXA_4) to a cellular test system (CHO cells) which generates a measurable read-out (GTP hydrolysis) upon modulation of the human ILM receptor of SEQ ID NO: 2 and (b) comparing the level of the read-out of the test system to a control level, wherein a difference in levels indicates whether the substance is an activator or an inhibitor of the receptor. In this case, the LXA_4 was an inhibitor. See Figure 2A for SEQ ID NO: 2. See p. 1697, paragraph bridging left and right columns, for assay. Takano et al. further teach that LXA_4 is an inhibitor of inflammation in a similar assay (p. 1699+, "*LXA_4 and 15-epi-LXA_4 Analogues Inhibit Mouse Ear Inflammation*").

Takano et al. do not teach use of MonoMac6 or THP-1 cells which had been stimulated with phorbol 12-myristate 13-acetate (PMA) and either LPS or smoke. However, the art recognizes that promonocytic cells such as MonoMac6 or THP-1 are

differentiated into activated macrophages by PMA and LPS. Such activated cells are known to be important in inflammation. See Hawkins et al., col. 27, lines 24-30.

Therefore, it would have been obvious to one of ordinary skill in the art at the time of the invention to modify the method of Takano et al. by substituting the PMA+LPS treated THP-1 cells of Hawkins et al. for the CHO cells of Takano et al. with a reasonable expectation of success. The motivation to do so is in Takano et al.'s disclosure that SEQ ID NO: 2 is important in inflammation, and the knowledge in the art that PMA+LPS activated THP-1 cells represent activated macrophages, which are known in the art to be important in inflammation.

Thus, the claimed invention as a whole was *prima facie* obvious over the combined teachings of the prior art.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Elizabeth C. Kemmerer, Ph.D. whose telephone number is (703) 308-2673. The examiner can normally be reached on Mon. - Thurs., 6:30 to 4:00, and alternate Fri.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne L. Eyler, Ph.D. can be reached on (703) 308-6564. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 872-9306 for regular communications and (703) 872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

ECK
January 27, 2003

Elizabeth C. Kemmerer

ELIZABETH KEMMERER
PRIMARY EXAMINER